Expert Reviews on Ophthalmology

Treatment of Ocular Allergies: Non-pharmacologic, Pharmacologic and Immunotherapy

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Abstract/Summary

Ocular allergy is a significant and growing issue worldwide but for many patients it is often not differentiated from systemic conditions such as hay fever. Management of seasonal and perennial allergic conjunctivitis is often poor. Management is principally through avoidance measures (blocking or hygiene), non-pharmaceutical (such as artificial tears and cold compresses) and pharmaceutical (such as topical antihistamines and prophylactic mast cell stabilisers). Vernal and atopic keratoconjunctivitis are more severe and generally need treatment with NSAIDs, steroids and immunomodulators. Giant papillary conjunctivitis can be related to allergy but also is often contact lens related and in such cases can be management by a period of abstinence and replacement of the lens or a change in lens material and/ or design. Immunotherapy can be efficacious in severe, persistent cases of contact lens or allergic conjunctivitis.

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Keywords

Ocular allergy; seasonal allergic conjunctivitis; perennial allergic conjunctivitis; vernal keratoconjunctivitis, atopic keratoconjunctivitis; giant papillary conjunctivitis; antihistamine; mast cell stabiliser; immunotherapy

Introduction

Allergic eye disease is the ocular manifestation of allergy, where the immune system produces an over-reaction or hypersensitivity to normally harmless substances known as allergens. The prevalence of allergy has shown a significant increase and appears to be plateauing across the world at a level between 15 and 20% [1, 2]. Although genetics plays an important role in susceptibility, the increase in prevalence is suggested to be the result of improved hygiene practices and increased antibiotic use as part of modern lifestyle and healthcare [3], in addition to environmental factors such as increased air pollution, climate change and increased planting and importation of allergenic plant species [4, 5]. Indeed, the effect of the environment is now considered a very strong influence on allergy prevalence – recent studies have shown that although migration to a new environment initially decreases prevalence in that area, it steadily increases to match that of the host country over time [6].

Of those who suffer from allergy, approximately 15-20% experience a form of ocular response [7, 8] and around 65% of those with rhinoconjunctivitis report ocular signs [9,10,11]. . However, several authors have pointed out that ocular allergies may be under-diagnosed and under-treated, particularly seasonal allergic conjunctivitis (SAC) where the ocular symptoms may fall under the umbrella of seasonal hay fever, which may underestimate its true prevalence [9,12, 13].. Ocular allergy encompasses a group of distinct clinical entities, typically confined to the conjunctiva, and includes allergic conjunctivitis (AC) which is subdivided into seasonal (SAC) and perennial forms (PAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC) and giant papillary conjunctivitis (GPC) [12].

Epidemiology

AC is a classic type I, IgE-mast cell mediated hypersensitivity disorder and the most common form of ocular allergy. SAC occurs on a seasonal basis, often as part of seasonal rhinoconjunctivitis (hay fever) and is most frequently caused by grass, tree and weed pollens and outdoor moulds which peak at different times of the year [12, 13, 14]. PAC occurs year round and is caused by house dust mites, animal dander, insects and indoor moulds [14]. The prevalence of AC is estimated to range from 15-20%, although recent studies suggest it may be as high as 40% [15]. However, SAC is far more common than PAC, making up 90% of all ocular allergic cases [16]. SAC is frequently associated with allergic rhinitis as part of hay fever (seasonal rhinoconjunctivitis) and is more common in children [15]. Predisposing risk factors include a history of atopy including eczema, asthma, and rhinitis [12, 15].

VKC is an uncommon condition that mainly affects young males (male to female ratio 2:1 to 4:1) in hot and dry countries occurring on a seasonal (spring) basis, although it may persist year round (23% of cases) [17]. Significant proportions recur during the winter (60% of cases) and 16% of seasonal cases develop in to perennial disease [17]. The exact prevalence is unknown. VKC usually occurs before 10 years of age, but generally resolves 4-10 years after initial onset [18]. Predisposing factors include a history of atopy [15, 16]. AKC is also uncommon, but the exact prevalence is unknown - one study estimated that 4.4% of over 1000 patients with ocular allergy had AKC [19]. AKC is considered to be the ocular component of atopic dermatitis (AD), with 20-40% of AD patients suffering from AKC

[10, 21]. AKC is more common in males and often occurs between the ages of 18 to 40 years [20, 21]. Predisposing factors include a history of atopy, atopic dermatitis and VKC in childhood [16, 20, 21].

GPC is typically associated with contact lens wear, with prevalence estimated to be 1-5% in contact lens wearers, but is reported to be as high as 20% [22]. It is more common in soft compared to rigid gas permeable (RGP) lenses (approximately 85% versus 15%) [22]. Risk factors include history of atopy, meibomian gland dysfunction, the presence of contact lens deposits, and poor lens fitting and design [22].

Pathophysiology

Both SAC and PAC are IgE-mast cell mediated hypersensitivity reactions, divided into two phases with the mast cell playing a central role [23, 24]. The reaction involves a complex series of immunological events coordinated by various mediators initiated by an allergen [25]. An allergen such as pollen reacts with specific IgE antibodies bound to a sensitised mast cell, triggering cross linkage of the IgE molecules and an influx of calcium ions into the mast cell. This causes the mast cell to degranulate and release preformed inflammatory mediators such as histamine which cause the signs and symptoms associated with the early phase response in sensitised individuals [12, 25]. The early phase response is immediate and lasts clinically for 20-30 minutes [26].

Mast cell degranulation also initiates a series of cellular and extracellular events which lead to the late phase response, including production of prostaglandins, thromboxanes and leukotrienes derived from arachidonic acid [14, 25]. Mast cells also release cytokines and chemotactic factors, which induce the production of IgE form B-cells, enhance production of CD4+ T-lymphocytes, attract eosinophils and activate vascular endothelial corneal and conjunctival cells to release chemokines (chemotactic cytokines) and adhesion molecules [14, 25]. The chemokines and adhesion molecules mediate the infiltration of eosinophils, basophils, neutrophils and CD4+Tlymphocytes to the site of inflammation and coupled with the newly formed mediators and sustained mast cell activation, they result in the late phase response [14, 25). This may occur 3-12 hours after the initial reaction, and symptoms can continue up to 24 hours [23]. The year round symptoms associated with PAC are the result of chronic mast cell activation and Th2-lymphocyte infiltration [14, 26].

Although not fully understood, VKC is considered a non-classic type I IgE mediated, CD4+lymphocyte driven allergic disorder involving mast cells and eosinophils [14, 17, 18]. An increased presence of sex hormone receptors in the conjunctiva of VKC patients and involvement of neural factors suggest that the pathogenesis of VKC is complex and multi-factorial in origin [17, 18]. The cause of atopic keratoconjunctivitis (AKC) is also not well understood. However, histopathogical and laboratory findings in AKC patients suggest that the pathogenesis of AKC is a complex non-classic type I IgE and eosinophil mediated allergic reaction involving mast cells and CD4+lymphocytes [14, 20, 21]. AKC may follow from childhood VKC – indeed, the clinical presentation is very similar and maybe considered a delayed manifestation of VKC [14].

Giant papillary conjunctivitis (GPC) is caused by a complex series of immunological inflammatory events and mechanical trauma to the palpebral conjunctiva typically by contact

lenses [22]. Ocular prostheses, extruding sclera buckles, exposed sutures and corneal deposits may also cause mechanical trauma [22]. Although not fully understood, inflammation is reported to be caused by type I hypersensitivity (with contact lens protein deposits and bacterial cell wall components as potential antigens), type IV delayed hypersensitivity mediated by T-cells which increases the inflammatory response, and mechanical trauma which releases chemotactic factors attracting neutrophils to the site of inflammation [14, 22].

Clinical Presentation

Signs and symptoms of SAC typically develop on a gradual basis, but can also develop suddenly following contact with the offending allergen [12]. They are often bilateral and include itching, tearing, eyelid oedema and conjunctival hyperaemia, chemosis and papillary reaction, with the severity varying with pollen count [12, 26]. Signs and symptoms of PAC are similar to SAC, but are milder and chronic in nature and may have occasional seasonal exacerbations [12, 13].

VKC is often bilateral (98% of cases) and signs include giant papillae on the palpebral conjunctiva (>1mm, with cobblestone appearance) or at the limbus, Tranta's dots (accumulation of eosinophils and epithelial cells), diffuse conjunctival hyperaemia, chemosis, and thick, white, stringy mucous discharge [17, 27]. Frequently the cornea is involved due to the close apposition of the palpebral conjunctiva, thus VKC has sight threatening potential. Corneal signs include superficial punctuate keratopathy, macro-erosion, shield ulcer, plaque formations and neovascularisation [18]. Occasionally conjunctival fibrosis and symblepharon may develop in severe cases [18]. Symptoms include intense itching, burning, watering, blurred vision, and difficulty opening eyes upon waking as eyelashes are matted together and photophobia [17, 18]. Complications of VKC include irregular astigmatism, keratoconus, hydrops, limbal hyperplasia [28]. Cataract and glaucoma may also occur following long term topical steroid therapy [18, 28].

AKC is a chronic, potentially blinding, bilateral condition. Signs include giant papillary hypertrophy and scarring of the palpebral conjunctiva (typically superior), chemosis and diffuse conjunctival hyperaemia [20, 29]. Limbal papillae may also occur and the eyelids of AKC patients are often thickened, erythmatous, fissured and crusting, and blepharitis (chronic staphylococcal) may be present [20, 29]. Corneal involvement includes superficial punctuate keratopathy, ulcer and plaque formation and as the condition progresses, corneal scarring and neovascularisation may develop [20, 29]. In addition the cornea may become thinned and atopic cataract may occur [25]. Symptoms include intense itching, burning, watering and photophobia [16, 20, 29].

GPC is often bilateral and is characterised by the presence of macropapillae (0.3-1mm in diameter) or giant papillae (>1mm) and hyperaemia on the superior palpebral conjunctiva [22, 30]. Other signs include increased mucous production and conjunctival oedema [22, 30]. Symptoms include burning, irritation and itching, of which the latter may increase on lens removal following manipulation of the eyelids causing mechanical stimulation of mast cells [22, 30]. With a contact lens in situ, there may be increased lens movement, and reduced comfort, vision and lens tolerance [22].

Non-pharmacological Treatment

The most important and most effective step in treating allergic eye disease is avoiding the offending allergen to prevent the hypersensitivity reaction from being triggered, but this necessitates the identification of the offending allergen and complete avoidance is not always possible [31]. In AC a detailed history is essential as knowledge of the period of time of year symptoms occur can allow identification using a pollen calendar to some extent, but peak levels of common causative pollens often overlap. The diagnosis of SAC and PAC is therefore mainly clinical [12, 32]. However, allergic challenge tests such skin prick and conjunctival provocation tests can be used to confirm diagnosis and detect the causative allergen, particularly those who do not exhibit the classic signs and symptoms upon examination, and where the causative allergen is ambiguous [26, 33]. However, although skin prick tests have a high sensitivity for systemic allergies, positive results in patients with ocular allergy have been reported to be as low as 20% [34]. This suggests that allergen specific IgE is produced locally (the eye), is responsible for allergic conjunctivitis and conjunctival tissue can be uniquely sensitised, confirming the need for specific and targeted treatment modalities [7, 25, 26].

Nonetheless, effective measures for allergen avoidance in SAC and PAC are based upon control of the environment. Given that pollens are the main cause of SAC, preventative measures include limiting outdoor activity during the symptomatic period, closing windows and using air conditioning when in a car or indoors, avoid touching/rubbing eyes after being outdoors, wash hands after being outdoors, wearing close fitting or wrap around style sunglasses when outdoors [35], wearing daily disposable contact lenses [36] and washing hair before sleeping. As PAC can affect the patient all year round, more thorough avoidance measures are necessary. Dust mite levels in the home can be reduced by using and regularly replacing protective pillow, mattress and duvet covers; washing bedding regularly at least at 60°C; vacuum and damp dust the entire house on a weekly basis; reduce humidity to between 35-50% and remove or regularly clean carpets, upholstery, curtains and any other objects that gather dust [35, 37, 38]. Animal dander can be reduced by eliminating all pets/animals from the home or keep them outdoors; regular vacuuming; minimising exposure to areas that gather animal dander; avoid touching animals; washing hands and avoid eye touching/rubbing after contact with animals; and washing all clothes that have come into contact with animals [35, 39]. Again, washing hair before going to bed can help remove any allergens trapped in the hair and prevent transfer to the pillow.

Other non-pharmacological interventions include the use of cold compresses, cooled preservative free artificial tears or saline, which help to wash out the allergens in the conjunctiva and encourage vaso-constriction of the blood vessels to reduce eyelid swelling, chemosis and hyperaemia [31, 40]. In addition, the artificial tears may act as a barrier to the pollen allergens to prevent the hypersensitivity response [16]. However, only very recently have these treatment strategies been supported with scientific evidence. A randomised, masked, crossover study found that artificial tears and cold compresses produced significant improvement in ocular redness, surface temperature, and subjective symptoms following conjunctival challenge compared to saline in patients with known grass pollen sensitivity [41]. Further, this effect was enhanced when they were used in combination; and was very similar to using the anti-allergy drug epinastine hydrochloride [41]. However, these findings

only apply during the active phase of disease, and further research is required to establish any prophylactic effect. Although there is a lack of evidence regarding their efficacy in other forms of ocular allergy such as VKC and AKC, their use appears plausible and these measures should be encouraged as supportive therapy, where they can be used between topical anti-allergic doses when symptoms persist or prior to the use of medication. Further, the use of sunglasses to minimise photophobia and protect the eyes from exposure to sun, wind and dust in VKC is advised [16, 17, 18].

Treatment of GPC is essentially non-pharmacologic in nature, where removal of the source of mechanical trauma and ceasing contact lens wear often brings about resolution within 4 weeks in moderate cases, but severe cases may take longer [22]. Patients should also be advised to avoid eye rubbing to prevent inadvertent mechanical mast cell degranulation. In contact lens related GPC (CLGPC), patients may continue to wear contact lenses following resolution if signs and symptoms allow and the cornea is not compromised [22]. Indeed, refitting after a period of lens wear cessation rather than during an episode of CLGPC is more successful in preventing recurrence (94% versus 78%) [22]. Refitting with new lenses of the same material has been found to reduce the recurrence of CLGPC by 61-66% but the refitting with a lens of different material or increasing the replacement frequency reduces the recurrence by 77-95% [42, 43]. Furthermore, changing to an RGP lens reduces recurrence by 80% - the smaller diameter reduces the area in contact with the palpebral conjunctiva and the lenses are easier to clean [22, 42]. It is essential to instruct a careful rub and rinse lens cleaning regime to minimise the build-up of surface deposits and in some cases enzymatic cleaning regimes may be required [22, 42].

Pharmacological Treatment

Complete allergen avoidance is not always possible and non-pharmaceutical treatments are not prophylactic and may not be sufficient to alleviate all signs and symptoms, so use of anti-allergic medication may become necessary. With increased knowledge of the pathophysiology of the hypersensitivity reaction in SAC and PAC over the years, there has been a rapid increase in the number of anti-allergic medications that target the immunological cells and inflammatory mediators involved in the allergic expression [7, 31, 44]. Ophthalmic anti-allergic medications include topical mast cell stabilisers, antihistamines, antihistamine-vasoconstrictor combinations and dual action agents with combined mast cell stabilising and antihistaminic properties [8, 26].

The most common agent used in the pharmacological management of allergic conjunctivitis is antihistamines and they are available topically for use alone, in combination with vasoconstrictors and in oral form. Antihistamines are competitive antagonists of histamine receptors (H1 and H2) on effector cells in the conjunctiva and eyelids [8, 45]. When stimulated by the main preformed mediator histamine, H1 receptors cause capillary dilation and increased vascular permeability which results in symptoms of itching and localised oedema typical of the hypersensitivity reaction [7, 25]. Therefore by the binding of these receptors by antihistamine, the inflammatory events normally initiated by histamine are prevented [44]. Topical ophthalmic preparations include azelastine hydrochloride 0.05% and emadastine hydrochloride 0.05%, which demonstrate efficacy in alleviating signs and symptoms of SAC with good safety profiles [46, 47, 48, 49]. Azelastine is also efficacious in

PAC [50]. More recently, bepotastine, a new selective H_1 receptor antagonist with twice daily dosing has been shown to significantly improve symptoms of itching and signs of ocular redness within 3 minutes and lasting for up to 16 hours in both randomised placebo controlled conjunctival allergen challenge and environmental studies [51—54]. Further, bepotastine 1.5% has also demonstrated improvements in non-ocular symptoms associated with conjunctival allergen challenge, including nasal congestion and rhinorrhea [55], suggesting it may be useful in patients who also experience generalised hay fever symptoms

Combination preparations include Otrivine-Antistin, containing the antihistamine antazoline 0.5% and the sympathomimetic (vasoconstrictor) xylometazoline 0.05%. Sympathomimetics stimulate adrenergic receptors causing capillary constriction and reduced blood flow and therefore reduce the hyperaemia, chemosis and eyelid swelling associated with the allergic response [56]. Naphazoline, another vasoconstrictor, either alone or in combination with witch hazel (naphazoline 0.01% w/v and witch hazel 12.5% v/v) a plant with reported astringent properties, is also available. Oral antihistamines should be considered alongside topical agents in SAC where it is associated with seasonal hay fever as the nose and throat are also affected in this condition [40, 56]. However, they are not as safe or effective as topically applied agents in treating allergic conjunctivitis [31, 56], and can cause drying of mucous membranes such as the conjunctiva, which may exacerbate symptoms and counter the washing action of the tears from removing allergens from the ocular surface [57]. However, several studies have demonstrated improved efficacy when they are combined with topical anti-allergic agents [58, 59, 60].

The mast cell stabilisers indicated for the treatment of allergic conjunctivitis include sodium cromoglycate 2%, nedocromil 2% and lodoxamide 0.1% and have demonstrated efficacy in alleviating the signs and symptoms of SAC and PAC compared to placebo [61, 62, 63]. Mast cell stabilisers work by preventing the degranulation of the sensitised mast cells thus inhibiting the release of inflammatory mediators and repressing the type 1 hypersensitivity reaction [7, 44]. This action results from preventing the calcium ion influx into the mast cell after antigen stimulation [7, 8, 44]. As mast cell stabilisers act on the mast cell before degranulation occurs, they will have no effect on the inflammatory mediators once they have been released [16]. Therefore mast cell stabilisers require a loading time of 10 to 14 days before symptoms are known to occur and are used topically as prophylactic agents [16, 31].

The dual action anti-allergic topical medications azelastine hydrochloride 0.05%, epinastine hydrochloride 500mg/mL, olopatadine hydrochloride 1mg/mL and ketotifen fumarate 250mg/mL combine both mast cell stabilising and antihistaminic properties and have demonstrated excellent efficacy and safety in treating SAC compared to a placebo [47, 64, 65, 66, 67] and can therefore have the advantage as both a prophylactic to prevent mast cell degranulation and a therapeutic agent to bring about symptomatic relief following the onset of symptoms [16, 31].

In severe SAC and PAC and cases unresponsive/refractory to conventional anti-allergic medications described above, anti-inflammatory agents may be necessary such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids [26, 31, 40]. NSAIDs work by preventing the formation of prostaglandins responsible for itching by blocking the cyclooxygenase pathway in the hypersensitivity response [16, 44]. Corticosteroids reduce inflammation by a variety of actions - they suppress the activation, recruitment and production of late phase inflammatory mediators; increase the availability of histaminases

(enzymes which break down histamine); prevent histamine production in mast cells; inhibit T-helpercell activity; and reduce the permeability of conjunctival blood vessels [16, 44].

The efficacy of the NSAIDs ketorolac trometamol 0.5% and diclofenac sodium 0.1% in treating allergic conjunctivitis compared to placebo has been demonstrated in several studies [68, 69]. Compared to levocabastine 0.05%, treatment efficacy with ketorolac 0.5% was similar in an environmental trial [70]; but less effective compared to emedastine and olopatadine in allergen challenge models [71, 72]. Treatment with corticosteroids requires careful monitoring owing to the potential increase in intraocular pressure and cataract formation [31]. With respect to topical NSAIDs, although saf in the vast majority of patients, they should not be prescribed to patients with aspirin hypersensitivity owing to several reports of inducing or worsening asthma attacks; or indeed to those with asthma and nasal polyps without confirmation of aspirin tolerability [73, 74, 75]. Immunomodulators such as cyclosporine are gaining increasing popularity in the long term treatment of severe allergic eye disease as an alternative to topical steroid therapy, particularly in VKC steroid responders [76, 77].

Immunotherapy

In severe, persistent cases of allergic conjunctivitis and those with systemic allergic associations, referral to an allergologist/immunologist may be necessary to initiate immunotherapy. It is a well-established and safe therapy with proven efficacy in a range of allergic conditions, particularly seasonal allergic rhinoconjunctivitis [78, 79]. Small doses of the offending allergen identified by skin prick and conjunctival provocation tests are often given sublingually over time to desensitise mast cells, essentially inoculating the patient [31, 78]. Even after discontinuation following 3-4 years of sublingual grass-pollen treatment, symptom scores remain low compared to those who have not received immunotherapy; corroborated by a reduction in inflammatory cell infiltration and interleukin expression following skin and ocular challenge test [80]. A recent Cochrane meta-analysis of 42 suitable clinical trials including nearly 4000 participants (allergic rhinoconjunctivitis or conjunctivitis) found that sublingual immunotherapy produced a significant improvement in ocular symptom scores for redness, itchiness and watery eyes compared to placebo; confirmed objectively with an increased allergen dose threshold for conjunctival response [81].

The use of subcutaneous injections (subcutaneous immunotherapy – SCIT) has also been shown to be effective in reducing symptomology in allergic rhinoconjunctivitis [82]. It is more effective with perennial rather than pre-seasonal conditioning, although the safety profile is similar [83]. No major side effects have been reported with doses as high as 120mu g [84]. It has been shown to be more effective than topical treatment both in terms of subjective symptoms and objective inflammation (serum immunoglobulin IgE) in vernal keratoconjunctivitis [85].

The use of epicutaneous therapy (patches) has shown a dose-dependent improvement in ocular and nasal symptoms in patients with allergic rhinoconjunctivitis; and therefore may be considered in patients who experience oral and gastrointestinal adverse events to sublingual therapy, or where low compliance is suspected [86]. Local immunotherapy by instillation to

the ocular surface has also shown improvement in symptoms of allergic conjunctivitis, including significant reduction in cytological findings following 1 year's treatment [87].

Immunotherapy for perennial allergic conjunctivitis is less well studied, but shows promise – a double blind clinical trial demonstrated a significant increase in the allergen threshold required to initiate an ocular allergic response in patients taking sublingual tablets for house dust mite allergy compared to a placebo [88]. There appears to be no clinical trials using immunotherapy in treating VKC, AKC or GPC.

Expert Commentary

It is clear that there is a wide range of anti-allergic available to manage SAC and PAC. However, the choice of whether to use a topical mast cell stabiliser or antihistamine is not clear since they are often similar in terms of efficacy and onset of action, although topical antihistamines provided relief sooner [89]. Interestingly, there appears to be no studies in the scientific literature examining the safety and efficacy of mast cell stabilisers and antihistamines in combination versus use of both alone and placebo where the results may prove useful to entry level optometrists who have access to few anti-allergic agents. Recent studies comparing the efficacy of dual action agents have shown conflicting results. Borazan *et al* (2009) compared the efficacy of olopatadine, ketotifen, epinastine, emedastine and the steroid fluorometholone in an environmental model and found no significant difference between the anti-allergic medications, but they were all superior to the steroid [90]. However, Lanier *et al* (2004) and Mah *et al* (2007) showed olopatadine superior to epinastine in conjunctival allergen challenge models [91, 92], but these conflicting results may be due to the different methodologies employed, with environmental studies suffering from a wide range of confounding factors, notably the lack of allergen exposure control [93]. More recently, alcaftadine 0.25% (antihistamine) has been shown to significantly improve ocular itching compared to placebo and to olopatadine 0.1% and 0.2% with an onset within 3 minutes of application; the major advantage being that alcaftadine requires only once daily dosing which may prove valuable in terms of increasing compliance and treatment success [94, 95]). Further, in a murine AC model, alcaftadine treated eyes demonstrated lower eosinophil infiltration in conjunctival epithelium compared to those treated with olopatadine; and had a protective effect on epithelial tight junction markers which would otherwise degrade due to allergic inflammation [96]. Compared to olopatadine 0.2%, alcaftadine 0.25% improves signs and symptoms to greater extent as early as 3 minutes post-allergen-challenge [97]. Bepotastine 1.5% has also been compared to olopatadine 0.2%, in a randomised, observer masked crossover environmental model – after 2 weeks of each treatment (2 drops bepotastine; 1 drop olopatadine), bespotastine produced significant reductions in ocular itching and itchy/runny nose compared to olopatadine based on symptom diary responses [98], Despite the twice daily dosing, over 66.7% of patients preferred to treat with bepotastine [98]. At present, no trials have compared alacftadine and bepotastine

Therefore, based on current evidence, the choice of which drug to prescribe should relate to the frequency of applications, cost and patient preference in addition to contraindications and potential interactions, rather than onset of action alone [89]. It is likely that dual action medications will become first line agents for the treatment of allergic conjunctivitis as they

demonstrate both prophylactic and therapeutic efficacy and require fewer applications. Simplifying the treatment regimen with these medications or alcaftadine compared to using traditional antihistamines and mast cell stabilisers separately serves to encourage patient compliance and offer patient convenience.

For VKC, the mast cell stabilisers sodium cromoglycate and lodoxamide, have been shown to be effective and are considered first line ophthalmological therapy as they can be used long term and have good safety profiles [99]. Mucolytics such as acetylcysteine are useful in breaking down the mucous discharge [15]. Bandage contact lenses are indicated for corneal ulcers to aid re-epithelialisation – preservative free topical anti-allergic medications, prophylactic antibiotics and ocular lubricants are necessary in these cases to prevent contact allergy/corneal toxic response/medicamentosa [16]. In severe cases topical steroid therapy is required but patients must be closely monitored due the potential risk of steroid induced cataract and glaucoma [17, 28]. Alternative medications in VKC steroid responders that have proved effective include immunomodulators such as cyclosporine and non-steroidal anti-inflammatory drugs such as ketorolac tromethamine, with the former helpful in re-epithelialisation of the cornea [99, 100]. Surgical intervention is necessary where VKC papillae are unresponsive to topical therapy and causing corneal ulcers or plaque formation [12, 13]. Papillae may be removed using CO_2 laser or cryotherapy [17, 27].

Treatment of AKC is similar to VKC. Long term therapy with topical mast cell stabilisers such as sodium cromoglycate, lodoxamide and nedocromil is required to treat the allergic inflammation in mild cases [16, 20, 101]. Cold compresses and artificial tears may help relieve the intense symptoms between doses, although evidence is lacking [16, 41]. In addition, systemic antihistamines may also be used particularly if other allergies are present. Any blepharitis should be treated with regular eyelid hygiene measures to remove bacteria and deposits from eyelids, and warm compresses to express the meibomian glands and help remove collarettes and crusting [102]. Topical antibiotic ointment such as 1% chloramphenicol is required if infection is present, but long term systemic tetracyclines may be required if conventional treatment is ineffective [102]. As with VKC, bandage contact lenses, ocular lubricants and prophylactic antibiotics are required for corneal ulcers [103]. Most cases of AKC require additional topical steroid therapy to relieve inflammation and symptoms – patients are closely monitored owing to the risk of steroid induced cataract and glaucoma [20, 21]. However, the immunomodulator cyclosporine may be used as an effective anti-inflammatory alternative in steroid responding AKC patients [104, 105].

In GPC, topical anti-allergic medication is not usually necessary, but mast cell stabilisers such as sodium cromoglycate are effective in moderate to severe cases [22, 106]. Approximately 75% of patients with moderate to severe CLGPC are treated with sodium cromoglycate 2% or 4% and (after a period of cessation) may continue contact lens wear [106, 107]. Steroid therapy is also indicated where therapeutic (bandage) contact lenses are required for corneal complications such as ulcer formation, but these are uncommon in GPC [16]. The multi action anti-allergic drug olopatadine may be used as an alternative treatment, with recent studies highlighting comparable efficacy to the topical steroid fluorometholone [108].

In patients with AC wanting to wear contact lenses, daily disposables offer a significant advantage over 2 weekly or monthly replacement lenses since frequent replacement helps to minimise allergen build-up on the lens surface, which may inadvertently prolong any

ocular allergic symptoms. In a crossover study, 67% of SAC patients experienced significantly reduced ocular symptoms compared to 18% when wearing monthly lenses during the allergy season; and objective signs (redness, papillae, ocular surface staining) also improved with daily disposables compared to baseline [109]. More recently, daily disposable lenses produced a significant reduction in signs of redness, papillae and ocular surface staining following airborne pollen challenge compared to no lens wear in sensitised patients – this effect was enhanced with the addition of lubricating agents to the lens material where reductions in symptoms of burning and itching were also observed [36].

Five-year Review

Over the next 5 years it is likely that better delivery devices for topical medication to the eye will become more common such as contact lens drug delivery. This type of drug delivery offers much benefit in terms of compliance and quality of life for patients with a range of chronic ocular conditions. Drug delivery from contact lenses could be utilised in conditions such as allergic conjunctivitis, glaucoma, dry eye and perhaps even age-related macular degeneration. While there have been scientific proof-of-concept publications [110], these have not yet led to commercial products. Part of this is presumably the regulatory complexity of combining a medical device (the contact lens) and a pharmaceutical agent.

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Key Issues

- Ocular allergy is a significant and growing issue for many patients, but is often not differentiated from systemic conditions such as hay fever
- Management of SAC and PAC is generally poor, with patients often self-medicating and rarely seeking an ophthalmic examination
- Avoidance of the allergen can be optimised through identification / use of pollen calendars, blocking (such as closing windows, using air conditioning and wearing wrap around spectacles) and hygiene (such as avoid touching/rubbing eyes, hand and hair washing) measures
- Research evidence for the efficacy of non-pharmaceutical treatments for acute ocular allergy management such as a cold compress and artificial tears is now available, although they have not been investigated in more severe VKC and AKC
- The mainstay of pharmaceutical treatment is dual action antihistamines and mast cell stabilisers as they combine an immediate and prophylactic mode of action
- NSAIDs, steroids and immunomodulators have a role in more severe disease with is unresponsive to other treatments
- Immunotherapy can be efficacious in severe, persistent cases of allergic conjunctivitis and those with systemic allergic associations
- Compliance/adherence is an issue with all topical medication and the future is likely to see the development of better delivery devices such as pharmaceutical releasing contact lenses

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* = of interest

** = of considerable interest

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